AWARD NUMBER: **W81XWH-17-1-0351**

TITLE: **Functional Characterization and Modeling of Acquired Resistance to Immune Modulation in Lung Cancer**

PRINCIPAL INVESTIGATOR: **Katerina Politi, PhD**

CONTRACTING ORGANIZATION: **Yale University**
**New Haven, CT 06511**

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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**14. ABSTRACT**
Immune checkpoint inhibitors (ICIs) that interfere with signals like PD-1, PD-L1 and CTLA4 that negatively regulate the activity of T-cells are now standard-of-care for the treatment of lung cancer. Response rates to these immune checkpoint inhibitors are modest (objective response rates are ~15-20% in unselected patients) but the *durability of the responses* is remarkable. Despite such prolonged responses, most of these patients with lung cancer are not cured and develop acquired resistance to the agents. *At present, we lack a comprehensive understanding of the cellular and molecular mechanisms that underlie acquired resistance to immune checkpoint inhibitors.* The overarching goal of this grant is to fill this knowledge gap and to identify and overcome acquired resistance to immune modulation in lung cancer by: 1) Establishing the genomic landscape of lung cancers with acquired resistance to ICIs and 2) Functionally characterizing mechanisms of acquired resistance to ICIs. Here we describe our progress towards achieving these goals including the analysis of resistant tumors, validation of resistance mechanisms and generation of new models to study resistance to immune checkpoint inhibitors. We also describe new therapeutic approaches that we are testing to overcome such resistance.

**15. SUBJECT TERMS**
Lung cancer, Immune checkpoint inhibitors, Resistance, Mouse Models, Antigen presentation

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**Functional Characterization and Modeling of Acquired Resistance to Immune Modulation in Lung Cancer**

## 1. INTRODUCTION

Immune checkpoint inhibitors (ICIs) that interfere with signals like PD-1, PD-L1 and CTLA4 that negatively regulate the activity of T-cells are now standard-of-care for the treatment of lung cancer. Response rates to these immune checkpoint inhibitors are modest (objective response rates are ~15-20% in unselected patients) but the *durability of the responses* is remarkable. Despite such prolonged responses, most of these patients with lung cancer are not cured and develop acquired resistance to the agents. *At present, we lack a comprehensive understanding of the cellular and molecular mechanisms that underlie acquired resistance to immune checkpoint inhibitors.* The overarching goal of this grant is to fill this knowledge gap and to identify and overcome acquired resistance to immune modulation in lung cancer by: 1) Establishing the genomic landscape of lung cancers with acquired resistance to ICIs and 2) Functionally characterizing mechanisms of acquired resistance to ICIs.

## 2. KEYWORDS

Lung cancer
Immune checkpoint inhibitors
Resistance
Mouse Models
Antigen presentation

## 3. ACCOMPLISHMENTS

Over the past year we have made significant progress on our proposed aims outlined below. During this first year we have focused on patient tumor sample collection and sequencing as well as development of reliable *in vivo* murine models of acquired resistance to immune checkpoint inhibitors (ICIs). We have also begun to examine the consequences of acquired resistance to immunotherapies on the tumor microenvironment via quantitative immunofluorescence and flow cytometry. This work has been supplemented with weekly immunosequencing meetings with collaborators at Yale University geared to studying human lung tumors treated with immunotherapies. In summary, to date this award has provided us with the strong impetus to continue to pursue clinically relevant questions related to immunotherapy resistance in lung cancer building on a manuscript in Cancer Discovery detailing our preliminary results (PMID: 29025772).

**What were the major goals of the project?**

| Major goals/tasks | Timeline (months) | % Completed |
|---|---|---|
| **Major Task 1:** Perform and analyze whole exome and RNA sequencing of 40 cases | 4-18 | ~50% |
| **Major Task 2:** Perform and analyze immunoprofiling of 40 cases | 18-24 | ~25% |
| **Major Task 3:** Test candidate resistance genes in vivo | 3-18 | ~50% |
| **Major Task 4:** Study the immune system in resistant mouse tumors | 6-18 | ~50% |
| **Major Task 5:** Test therapeutic strategies to overcome resistance | 12-24 | ~10% |

**What was accomplished under these goals and what do you plan to do during the next reporting period to accomplish the goals?**

For each of the goals proposed, the following progress has been made in the last year:

**Specific Aim 1: Establish the genomic landscape of lung cancers with acquired resistance to ICIs.**

**Major Goal 1.** Perform and analyze whole exome and RNA sequencing of 40 cases

As proposed we have been collecting tumor samples and processing them for DNA and RNA sequencing. We have performed whole exome sequencing of 23 cases and RNA sequencing of 19 cases in the first year of this award (58% and 48% completed of what was proposed for the two-year award, respectively). Quality control measures have been successfully implemented to limit sample inclusion to tumors with >20% purity and strict radiographic evidence of response and resistance. Initial bioinformatic analysis including mutation calling and copy number analysis was completed on-schedule during the first year of funding on these cases. Whole exome sequencing did not detect any recurrent mutations or copy number alterations in our cohort of cases with acquired resistance to immunotherapy. However, we have found acquired alterations in pathways that we and others have implicated in resistance to immune checkpoint inhibitors like MHC I antigen presentation. Our studies will be very important to functionally validate the genetic alterations observed in mouse models of immune checkpoint inhibitor resistance. Initial RNA sequencing analysis of this cohort has revealed the presence of an inflammatory tumor microenvironment with significant upregulation of the inhibitory receptor LAG-3 at immune checkpoint inhibitor resistance. Whole exome sequencing of and additional 17 tumors and RNA sequencing of 21 tumors will be performed to complete the cohort and will be followed by a comprehensive informatic analysis of the data.

**Major Goal 2**. Perform and analyze immunoprofiling of 40 cases

Histological analysis of immune cell profiles in tumors with acquired resistance to immune checkpoint blockade is currently ahead of schedule. This work was proposed to be completed in the last 6 months of second year of this award. Already 8 pairs of matched tumors pre- and post-acquired resistance to immunotherapy have been interrogated with multiplexed quantitative immunofluorescence for localized measurements of the immune inhibitor receptors PD-1, LAG-3, TIM-3 and the T cell activation markers Ki-67 and GZMB in CD3+ T lymphocytes. Consistent with the RNA sequencing data, we found upregulation of LAG-3 in five of eight cases examined (**Figure 1**). PD-1 was also upregulated in the majority of cases while TIM-3 levels were only increased in three of eight cases at acquired resistance. In most cases, Ki-67 was uniformly upregulated in T cells in the acquired resistance specimens compared to pre-treatment cases while GZMB showed a more variable pattern. Overall these data support the presence of a more inflammatory microenvironment in tissues following treatment with the immune checkpoint inhibitors compared to pre-treatment specimens. In the upcoming year of this award, we will continue to process and stain 32 additional samples as indicated in our proposal. In addition to the tumor infiltrating lymphocyte panel of antibodies that we have already optimized for multiplexed tissue analysis, in the

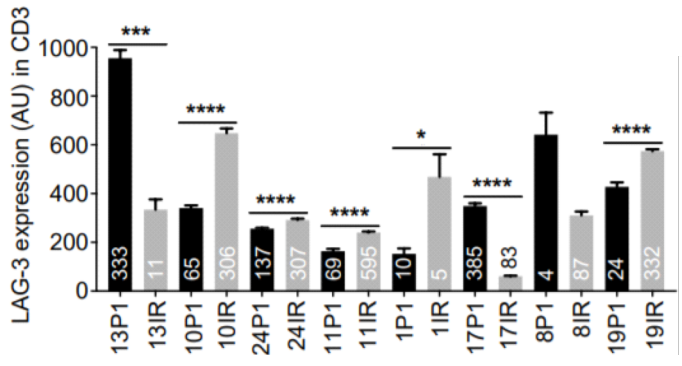



**Figure 1. Tumor immunoprofiling of T-cell inhibitory marker, LAG-3, in tumor tissues from patients pre-immunotherapy and at resistance to ICIs.** Quantitative immunofluorescence analysis showing the levels of the immune inhibitory molecule LAG-3 in CD3 positive tumor infiltrating lymphocytes (TILs) in paired pre- and post-immunotherapy tumor samples as quantified using the AQUA® software. Numbers in the individual bars represent total fields of view analyzed. Statistical significance was calculated using the Mann-Whitney test. P1- pre-immunotherapy and IR- immunotherapy resistant. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05

upcoming year we will also add panels for other components of the tumor microenvironment, such as cells of myeloid lineage.

**Specific Aim 2: Functionally characterize mechanisms of acquired resistance to ICIs.**

**Major Goal 3**. Test candidate resistance genes *in vivo*.

After whole exome sequencing was completed on 14-ICI-resistant lung cancer samples, in silico analysis identified a variety of novel mechanisms of acquired resistance to immune checkpoint inhibitors, including mutations and copy number alterations in genes encoding components of the HLA Class I antigen processing and presentation machinery. Among the findings was one case of acquired homozygous copy loss of *B2M* that resulted in lack of HLA class I expression on the cell surface in both the patient's tumor sample and a corresponding patient-derived xenograft (PDX). Downregulation of B2M was also found in two additional PDXs established from immune checkpoint inhibitor resistant tumors. We tested if B2m expression confers sensitivity to immune checkpoint inhibitors *in vivo*, we used a CRISPR-mediated approach to knockout *B2m* in a Kras mutant, immune checkpoint inhibitor sensitive, murine lung cancer cell line (UN-SCC680AJ) and transplanted the cells into a syngeneic, immunocompetent mouse. We found that the *B2m* knockout tumor was resistant to immune checkpoint inhibitor therapy in contrast to the wild type cells. This data provides evidence for the disruption of HLA Class I antigen processing and presentation as a mechanism for escape from immune checkpoint inhibitors in lung cancer and provides information on the immune microenvironment in immune checkpoint inhibitor resistant tumors. The establishment of this platform has provided a system that can now be readily used to further investigate the functional role of genomic alterations found in immunotherapy resistant tumors, such as mutations in antigen presentation machinery and interferon pathway genes. Work is currently underway to functionally evaluate additional potential mechanisms of acquired resistance including alterations found in members of the proteasome pathway (including PSMD7) that were discovered as a result of our sequencing efforts. To this end, we have already successfully modeled one additional alteration (PTEN loss) *in vivo* (**Figure 2***)*. In our lung tumor model, we observed that PTEN loss contributes to resistance to immune checkpoint blockade. Therefore, importantly we now have two models of resistance to immune checkpoint inhibitors arising as a result of different resistance mechanisms that can be used as platforms to test new therapies. Over the next year we will work to further our understanding of the mechanism behind these resistance phenotypes, as well as functionally validate other candidates of resistance to immune checkpoint blockade *in vivo*.

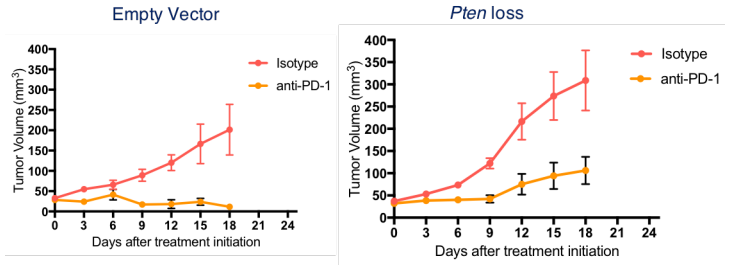
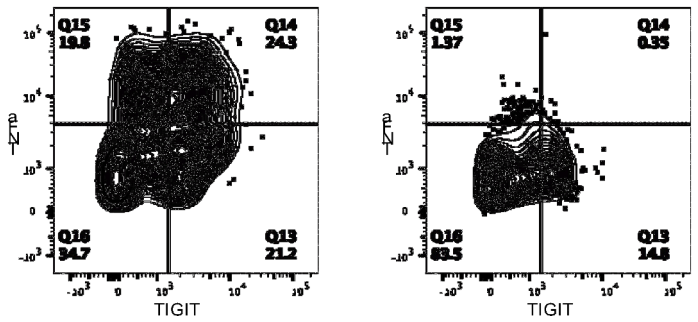



**Figure 2. Pten loss confers resistance to anti-PD-1 therapy in vivo**. 5x10$^5$ UN-SCC680AJ cells from Pten null cells (right) and vector control (left) cells were injected into the dorsal flanks of A/J mice subcutaneously. Tumors were allowed to grow to approximately 30 mm$^3$ before administration of 100µg of anti-PD-1 or isotype control via intraperitoneal injection every 3 days. The size of the tumors in the Pten wild-type and Pten knock-out lines treated with anti-PD1 are shown.

**Major Goal 4.** Study the immune system in resistant mouse tumors

UN-SCC680AJ B2m knockout tumors established *in vivo* which harbor resistance to immune checkpoint blockade have undergone initial profiling via flow cytometry during the first year of this award as proposed (month 3-6). We found in this model that immunotherapy resistant tumors (UN-SCC680AJ B2m knockout) have fewer

total tumor infiltrating CD8 T cells and myeloid cells as compared to UN-SCC680AJ wild-type tumors. We also observed that the CD8 T cells in the immunotherapy resistant tumors (UN-SCC680AJ B2m knockout) were less proliferative and produced less IFNγ, TNFα, and Granzyme B. We have also assessed the quantity and quality of NK cells in these B2m deficient, immunotherapy resistant tumors. Interestingly, while we observed no change in the total number of NK cells in tumors with B2m loss, we did notice that B2m null, tumor-infiltrating NK cells had lower TIGIT and TNFα expression, indicative of reduced activation (**Figure 3**). Based on this observation, further work is ongoing and will continue over the next year of funding (month 6-24) to assess the functional role of NK cells in the maintenance of the immunotherapy resistance phenotype. To this end, we will begin testing a few pre-clinical therapeutic options to assess the possibility of re-activating NK cell activity in the B2m deficient, immunotherapy resistant setting.




**UNSCC680AJ B2M-WT**
*Immunotherapy sensitive*

**UNSCC680AJ B2M-KO**
*Immunotherapy resistant*

**Figure 3. NK cells from B2m null, immunotherapy resistant lung tumors are less activated.** B2m knockout UN-SCC680AJ tumors were harvested and stained for flow cytometry analysis. Representative data is shown here. Tumor infiltrating NK cells were identified and stained for activation markers such as TNFα and TIGIT.

**Major Goal 5.** Test therapeutic strategies to overcome resistance

Efforts to test strategies in overcoming resistance to immunotherapies *in vivo* were proposed to be completed during the second year of this award and will be a priority for us in the upcoming year. These studies will test the efficacy of boosting NK cell function through CD137 co-stimulation, TIGIT blockade, and cytokine therapy (DR-IL-18) in addition to targeting alternative checkpoint blockade molecules, such as TIM-3 and LAG-3. In preliminary data, we have found that DR-IL-18 can lead to the regression of B2m null tumors. We are currently repeating and confirming these results but this would represent an important step towards developing a strategy to overcome resistance in tumors with defects in MHC I antigen presentation. During the upcoming year we plan on extending these therapeutic studies and comparing the effects of the therapies in tumors that have different resistance mechanisms (e.g. B2m vs. Pten loss).

**What opportunities for training and professional development has the project provided?**

The project has provided opportunities for trainees in the PI's lab and collaborators to learn and work on Cancer Immunology. Dr. Hastings, for example, who is trained as a cancer biologist, has gained significant expertise in Cancer Immunology by studying problems tackled in this grant. She has also attended the AACR Tumor Immunology and Immunotherapy meeting in Boston in 2017. Camila Robles-Oteiza attended the CSHL Mechanisms and Models of Cancer meeting which was valuable for her professional development. Perhaps most importantly this grant has provided everyone on the team the opportunity to work collaboratively on an important scientific question and capitalize on the value of multidisciplinary team research. This will continue in the upcoming year of the award.

**How were the results disseminated to communities of interest?**

The results were disseminated to audiences mainly through presentation of the results at National and International Conferences as described below in section 6. Moreover, the PI has talked about the work in various Outreach settings, for example a science café called Tilde Café.

## 4. IMPACT

Nothing to report

## 5. CHANGES/PROBLEMS

Nothing to report

## 6. PRODUCTS

### Publications

Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. **Gettinger** S, Choi J, Hastings K, Truini A, Datar I, Sowell R, Wurtz A, Dong W, Cai G, Melnick MA, Du VY, Schlessinger J, Goldberg SB, Chiang A, Sanmamed MF, Melero I, Agorreta J, Montuenga LM, Lifton, R, Ferrone S, Kavathas P, Rimm DL, Kaech SM, Schalper K, Herbst RS, **Politi** K. Cancer Discov. 2017 Dec;7(12):1420-1435. doi: 10.1158/2159-8290.CD-17-0593. Epub 2017 Oct 12. PMID:29025772. Published. This manuscript is directly relevant to the work in this grant but was accepted shortly after the grant was initiated therefore support from this grant is not acknowledged.

### Presentations

2018: World Conference on Lung Cancer, Toronto, Canada.

2018: SITC Immunotherapy Responsiveness Workshop, San Francisco, CA

2018: AACR Annual Meeting, Chicago, IL

2018: British Columbia Cancer Agency Seminar Series, Vancouver, Canada.

2018: AACR-SNMMI meeting, San Diego, CA.

2018: Fifth AACR-IASLC International Joint Conference on Lung Cancer, San Diego, CA.

2017: New York Cancer Genome Network Meeting, New York, NY.

2017: Society for the Immunotherapy of Cancer, National Harbor, MD.

2017: AACR Advances in Modeling Cancer in Mice: Technology, Biology, and Beyond, Orlando, FL, “

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**a. What individuals have worked on the project?**

| | |
|---|---|
| Name: | ***Katerina Politi,*** *no change* |
| Name: | ***Anna Wurtz,*** *no change* |
| Name: | ***Robert Homer,*** *no change* |
| Name: | ***Scott Gettinger,*** *no change* |
| Name: | ***Roy Herbst,*** *no change* |
| Name: | ***Kurt Schalper,*** *no change* |
| Name: | ***Hongyu Zhao,*** *no change* |

| | |
|---|---|
| Name: | ***Katherine Hastings*** |
| Project Role: | *Post-doctoral Associate* |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | *6* |
| Contribution to Project: | *Dr. Hastings generated the UNSCC680AJ B2m and Pten knock-out cell lines and performed the syngeneic subcutaneous lung tumor experiments as outlined in Specific Aim 2 of the proposal. She also is working on the analysis of data from resistant tumors collected in Specific Aim 1.* |
| Funding Support: | *NIH/NCI* |
| Name: | ***Camila Robles-Oteiza*** |
| Project Role: | *Graduate Student* |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | *2* |
| Contribution to Project: | *Ms. Robles-Oteiza is currently working on the syngeneic subcutaneous lung tumor experiments outlined in Specific Aim 2 using the LKR13 and 368T1-TGL cell lines.* |
| Funding Support: | *Yale University* |
| Name: | ***Nicholas Rashleigh*** |
| Project Role: | *Post-graduate Research Associate* |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | *3* |
| Contribution to Project: | *Mr. Rashleigh manages the animal colony including the mice allocated to this research project.* |
| Funding Support: | *NIH/NCI* |
| Name: | ***Susan Kaech*** |
| Project Role: | *Co-Investigator (changing now to Collaborator)* |
| Researcher Identifier (e.g. ORCID ID): | |

| | |
|---|---|
| Nearest person month worked: | *1* |
| Contribution to Project: | *Dr. Kaech provided oversight, guidance and her expertise in T-cell biology and co-signaling as they related to the proposed experiments and the data generated. Dr. Kaech recently relocated to the Salk Institute in La Jolla, CA. Her role is as a collaborator now rather than a co-investigator and will not receive funds.* |
| Funding Support: | *NIH/NIAID*<br>*NIH/NCI*<br>*Cancer Research Institute*<br>*Melanoma Research Alliance* |
| Name: | ***Victor Du*** |
| Project Role: | *Post-doctoral Associate* |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | *1* |
| Contribution to Project: | *Dr. Du worked closely with Dr. Hastings to analyze the data from the UNSCC680AJ B2m knock-out in vivo experiments. He works in Dr. Kaech's lab in La Jolla, CA at the Salk Institute and collaborates with us on this project.* |
| Funding Support: | *Cancer Research Institute* |

**b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Listed below are updates to the active other support of the key personnel on the project: Katerina Politi (PI), Susan Kaech (Co-Investigator) and Robert Homer (Pathologist), since this award was activated on September 1, 2017. Table 1 provides a status update of the active and pending awards that were reported at the time of this award's activation. Table 2 provides information on awards that were activated during the course of this award, but had not been previously reported as "Pending Support" at the time of this award's activation.

Table 1. Updates to funding support status reported at the time of award activation

| Investigator | Funding Agency | Award Number | Project Title | Status at Time of Award Activation | Current status |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Politi, Katerina | NIH/NCI | 3P50CA196530-02S1 | Epigenetic Control of Resistance to Targeted Therapies in Lung Adenocarcinomas | Active | Completed 07/31/2018 |
| Politi, Katerina | Roche | N/A | Roche pRED Cancer Immunotherapy and Yale University Collaboration | Active | Completed 04/30/2018 |
| Politi, Katerina | NIH/NCI | R01CA195720 | Targeting the Immune System in Mouse Models of Lung Adenocarcinoma | Active | Completed 03/31/2018 |
| Politi, Katerina | Roche/Genentech | YAL-4-PL40440 | Transforming the Immune Desert into an Immunostimulatory Microenvironment in Lung Cancer | Pending | Active 08/20/2018 |
| Kaech, Susan | Roche | N/A | Roche pRED Cancer Immunotherapy and Yale University Collaboration | Active | Completed 04/30/2018 |
| Kaech, Susan | NIH/NCI | R01CA195720 | Targeting the Immune System in Mouse Models of Lung Adenocarcinoma | Active | Completed 03/31/2018 |
| Kaech, Susan | NIH/NIAID | R37AI066232 | Regulation of Memory T Cell Development | Active | Completed 01/31/2018 |
| Kaech, Susan | Yale-Gilead | YG-013-15 | New Targets for Cancer Immunotherapy | Active | Completed 12/31/2017 |
| Kaech, Susan | Melanoma Research Foundation | N/A | Mechanisms Controlling Melanoma Dormancy and Metastatic Progression | Active | Completed 09/30/2017 |
| Kaech, Susan | NIH/NCI | P50CA196530 | Identification of Neoantigens for Identifying and Tracking Tumor Specific T cells | Active | Completed 07/31/2017 |
| Kaech, Susan | NIH/NCI | R01CA206483 | Lipid Metabolism, Inflammation, and T Cell Dysfunction in HIV-Associated Cancer | Pending | Active 06/01/2018 |
| Homer, Robert | NIH/NCI | R01CA195720 | Targeting the Immune System in Mouse Models of Lung Adenocarcinoma | Active | Completed 03/31/2018 |
| Homer, Robert | NIH/NCI | 3P50CA196530-02S1 | Epigenetic Control of Resistance to Targeted Therapies in Lung Adenocarcinomas | Active | Completed 07/31/2018 |
| Homer, Robert | State of Connecticut Department of Public Health | N/A | Molecular Imaging of the Lung | Active | Completed 09/30/2017 |

Table 2. Additional funding support activated and completed during the course of the current award

| Investigator | Funding Agency | Award Number | Project Title | Award Activation Date |
|---|---|---|---|---|
| Politi, Katerina | AACR Stand Up to Cancer | N/A | Functional Characterization and Modeling of Acquired Resistance to Immune Modulation and Targeted Therapy in Kras-driven Lung Cancer | 08/01/2017 (Completed 07/31/2018) |
| Politi, Katerina | Symphogen | N/A | Pre-clinical Assessment of the Efficacy of Sym004 in EGFR Mutant Lung Cancer | 01/01/2018 |
| Politi, Katerina | American Lung Association | N/A | Targeting Cancer Metabolism in Therapy Resistant EGFR Mutant Lung Cancer | 10/01/2016 |
| Kaech, Susan | NIH/NCI | R01CA216101 | Mitochondrial Heterogeneity in Melanoma Tumor and Immune Responses | 09/01/2018 |
| Kaech, Susan | Cancer Research Instistute | N/A | Elucidating Cellular and Genetic Factors Associated with Tumor Resistance to Immunotherapies | 03/01/2018 |
| Kaech, Susan | NIH/NIAID | R37AI066232-14 | Regulation of Memory CD8 T Cell Development | 02/16/2018 |

**c. What other organizations were involved as partners?**

O**rganization Name:** The Salk Institute

**Location of Organization:** *La Jolla, CA*

**Partner's contribution to the projec**t: Collaboration with Dr. Susan Kaech

## 8. SPECIAL REPORTING REQUIREMENTS

Not applicable.

## 9. APPENDICES.

No appendices.